APPENDIX VIII

COMPARISON OF HUMAN UPTAKE AMONG CIGARETTE BRANDS RATED AS ONE MILLIGRAM TAR YIELD

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SUMMARY

Several reports have shown the trend toward reduced carbon monoxide, nicotine, and tar yields of cigarettes over approximately the last 30 years. Concomitantly, reports of epidemiological studies have shown that individuals who have selected cigarette brands which standard smoking machine tests classify as ultra low yield brands have significantly fewer diseases related to smoking. While the smokers of the ultra low yield brands seem to benefit; the non-smoker benefits substantially from not smoking.

This report presents an analysis of data gathered from a large sample of regular smokers of ultra low tar yield cigarette brands. Since smoking behavior is recognized as a determinant of an individual smoker's uptake of both nicotine and tar, the large number of subjects studied greatly increases the value of the data derived from these studies. The experimental design allowed comparison of the plasma cotinine concentration obtained from smokers who were only minimally influenced by factors other than those normal to their own natural environment. Only those factors which normally affect smoking behavior and thus nicotine uptake would be expected to operate. Correction for daily cigarette consumption or for other factors which might alter nicotine uptake and thus tar intake on an individual cigarette basis were not included in the analysis. The plasma cotinine concentrations used in the analysis represent the total smoking experience of the individual during the period of smoking each brand represented in the study.

The major points made as a result of this analysis are:

1. Individuals differ greatly in their plasma cotinine concentration despite comparable consumption of numbers of cigarettes. Reasons are presented for this difference in the discussion section of the report.
2. Individuals with high plasma cotinine concentrations while smoking one brand tend to have high plasma cotinine concentrations on all brands investigated. The same statement is true for individuals with low plasma cotinine concentrations.
3. On the average a smoker's plasma cotinine concentration is proportional to the brand yield values obtained by measurement utilizing the standard smoking machine procedures.
4. If the individuals who obtain greater than average yield are considered to be a problem then these data support the conclusion that all ventilated filter cigarette brands share in the problem.
5. The large number of smokers who obtain lower than average plasma cotinine concentrations while smoking ultra low tar cigarette brands benefit from the reduced nicotine and thus tar intake.

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INTRODUCTION

The nicotine and tar rating of cigarettes as determined by a standard smoking machine method (FTC test method) are published for the various cigarette brands. Several brands are reported to be ultra low yield brands. These brands yield one milligram tar or less by the standard smoking machine test. The individual delivery of these brands is known to be affected by smoking behavior. It is generally accepted that increased cigarette consumption will increase nicotine and tar intake. The number of puffs taken per cigarette and the depth of inhalation are also recognized as factors that increase individual uptake of nicotine and tar.

Several reports, notably the report of Wald, Doll and Copeland, 1981, have shown the trend toward reduced carbon monoxide, nicotine, and tar yield of cigarettes over the past 30 years. Concomitantly, reports of epidemiological studies have shown that a significant reduction in the incidence of diseases related to smoking has accompanied the reported reduction in these substances. More recently filtration that includes air dilution has been used to markedly reduce potential cigarette delivery of nicotine, tar and carbon monoxide. Individuals who have selected cigarette brands which standard smoking machine tests classify as ultra low yield brands have statistically significant fewer diseases related to smoking than individuals who have remained as full flavor cigarette smokers. While the smokers seem to benefit from the reduced deliveries of cigarettes marketed today, the non-smoker benefits more as is evidenced by the very significant reduction in diseases related to smoking in the non-smoker population.

Investigators have reported that smokers who switch to the ultra low brands may increase their consumption or change their pattern of smoking to compensate for the reduced yield of the cigarettes. In addition questions have arisen as to the relative human uptake of nicotine and tar as a result of smoking the various brands which have different types of air dilution filters.

This report presents an analysis of data gathered from a large sample of regular smokers of air dilution filtered cigarettes which are classified as ultra low tar delivery cigarette brands by the FTC smoking machine method. The analysis presents evidence which supports the concept that inter-individual differences in nicotine uptake occur among smokers. The data supports the conclusion that there is no difference in the delivery of nicotine and thus tar to individual smokers as a result of changing brands from one type of air dilution filter to another type of filter.

METHODS

The investigation utilizes measurements of plasma cotinine concentration. Cotinine is a major metabolite of nicotine. Nicotine is a basic substance and like many amine compounds the concentration of the free base and the degree of ionization provides for rapid tissue or organ distribution of the compound. The intracellular ionization and low free base concentration prevents rapid redistribution of the compound to the

plasma compartment. Thus, measurement of plasma cotinine concentration made at a time other than at steady state, may not accurately reflect total body nicotine concentrations. Since distribution and excretion of nicotine are highly pH dependent, measurement of nicotine half-life and calculation of "apparent volume distribution" varies among individuals (Benowitz, N. L. et al, 1982). The substantial inter-individual difference in these parameters limits the usefulness of plasma nicotine concentration a a measure of nicotine uptake. The large apparent volume of distribution for nicotine greatly reduces the plasma concentration and adds to the complications associated with measuring plasma nicotine concentration.

Cotinine is more water soluble than nicotine and the apparent distribution is less affected by pH differences. Cotinine has a half-life that is said to be approximately 24 hours as compared to the reported two hour half-life of nicotine. Therefore, while the plasma nicotine concentration only reflects delivery of the last few cigarettes, plasma cotinine concentration determined under steady state conditions will be only minimally affected by the smoking experience with the last few cigarettes. Thus, measurement of plasma cotinine concentration provides a method for measurement of the nicotine and tar uptake as a result of an individual's smoking experience in the subject's natural daily environment. The data obtained includes both factors related to cigarette delivery and individual smoking behavior.

The determination of plasma cotinine concentration as a sensitive measurement of nicotine uptake is discussed in detail in a paper prepared by Doctor J. van Rossum.

This analysis includes data obtained from 288 smokers of ultra low tar cigarette brands. Individuals were recruited into the study by random sample interview in shopping centers and by newspaper advertisement. Only smokers who stated they smoked approximately 20 or more cigarettes per day were selected. An attempt was made to recruit equal numbers of males and females into the study.

STUDY DESIGN:* Smokers of either Barclay brand or Carlton brand cigarettes were selected for study since these two brands represented the preference of a majority of the persons interviewed. The Barclay brand cigarette is equipped with an Actron air dilution filter while the Carlton brand is equipped with a conventional air dilution filter. Baseline data included body weight and number of cigarettes smoked per day. A blood sample was obtained for measurement of plasma cotinine concentration.

The subjects continued to smoke their usual cigarette brand. At the end of 7 days blood samples were obtained for measurement of plasma cotinine concentration. During the period the subjects were asked to keep a diary which indicated number of cigarettes smoked and time of the day at which the cigarette was smoked. The subjects were asked to refrain from use of tobacco products other than smoking the brand they had been smoking for at least the last three months. On the average the subjects had smoked one brand of ultra low tar deliver for at least six months.

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*These studies were carried out under the direction of Doctor Gio Gori at the Franklin Institute, Silver Spring, Maryland.

After the two week baseline period the Carlton smokers were switched to Barclay brand the Barclay smokers were switched to the Carlton brand. At the end of 7, 14, and 21 days on the new brand blood samples were obtained for determination of plasma cotinine concentration. During this three week period a diary was kept which indicated number of cigarettes smoked and the time of day at which the cigarette was smoked. On the average the smokers consumed 30 cigarettes per day for the three week period. The average of the three plasma cotinine concentrations for this three week period would be the result of smoking approximately 630 cigarettes.

After completion of the three week cross-over study, all the subjects were switched to Cambridge brand cigarettes. The Cambridge brand is equipped with a conventional air dilution filter. The smokers remained on Cambridge brand for two weeks. Blood samples for determination of the plasma cotinine concentration were obtained on days 7 and 14 following the switch to the Cambridge brand. Thus, the plasma cotinine concentration measured during this last two week period could serve for comparison with the plasma cotinine concentration measurement obtained from the subject during his baseline period and the data obtained during the cross-over period.

All cigarettes provided to the subjects were purchased from commercial distributors, each brand coming from he same production batch, thus minimizing variance. The data obtained from the standard smoking machine test (FTC method) for the batch of each brand used in the study are summarized in Table 1.

The plasma cotinine concentrations and other data were supplied to us by Doctor Gori and we were asked to provide an analysis of the data. The experimental design allowed comparison of the plasma cotinine concentration obtained from smokers who were only minimally influenced by factors other than those normal to their own natural environment. Those factors which normally affect smoking behavior and thus nicotine uptake would be expected to operate. The study design provided for the steady state conditions required for comparison of pharmacokinetic parameters as stressed by J. van Rossum, 1982. The cross-over and switch design allowed study of delivery of each brand in an individual smoker thus minimizing inter-individual differences in nicotine metabolism.

Our analysis included scattergram preparation which allowed comparison of plasma cotinine concentration obtained from individual smokers during their experience with each brand. Regression analysis and factor analysis were included in this study of the data. The figures that show the regression analysis also contain a line which provides for slope analysis that compares the maximum uptake of nicotine and thus tar for the individuals studied. Ninety percent of the smoker's studied gave uptake values less than the slope of this line times the uptake value obtained when the individual smoked the Cambridge brand.

The data are plotted as a log normal distribution. The cumulative percent of population sample providing a plasma cotinine concentration is plotted vs. the log of the value obtained for the plasma cotinine concentration. This log distribution plot was used to compare the deliveries of the cigarette brands equipped with the conventional air filter to the deliveries obtained from cigarettes equipped with the Actron filter.

RESULTS

The data showed wide inter-individual differences in plasma cotinine concentration. The number of cigarettes smoked per day averaged 30, and varied between less than 20 and more than 35. Neither daily cigarette consumption ($r^2 = 0.09$) nor the reciprocal of body weight ($r^2 = 0.01$) was significant in determining plasma cotinine concentration, over all smokers on all brands. There was a trend for increased plasma cotinine concentration to occur within individuals based upon daily cigarette consumption, however, variation in cigarette consumption was small and therefore the factor was of little use in the analysis.

Therefore, a method of analysis was used which allowed comparison of brand effects in a given individual, and thus inter-individual differences were avoided. The total smoking experience with each brand studied was included in the analysis. Corrections for daily cigarette consumption or other factors which might alter nicotine uptake and thus tar intake on an individual cigarette basis were not included in the analysis. The plasma cotinine concentrations shown in the figures represent the total smoking experience for that period of the study.

Figure 1. is a scattergram which indicates the plasma concentration differences for the individual smokers while smoking either Barclay or Carlton brand cigarettes. These data are derived from the cross-over period therefore the brand experience is new for each group. Table 2 provides the number of individuals and the percent of the total found in each of the four quadrants. The four quadrants were derived by providing a line at the average concentration obtained while smoking the brand indicated. Therefore, Quadrant I contains individuals who gave higher than average plasma concentrations of cotinine while smoking the Carlton brand and lower than average plasma concentrations of cotinine while smoking the Barclay brand. Quandrant II contains those individuals who gave higher than average cotinine plasma concentrations while smoking either brand. Quadrant III is composed of the individuals who gave higher than average concentration for plasma cotinine while smoking the Barclay brand and lower than average plasma concentrations for cotinine while smoking the Carlton brand. Quadrant IV contains the individuals with below average concentration of plasma cotinine while smoking either brand. It is interesting that more than three-fourths of the individuals tested are found in either Quadrant II or Quadrant IV. There was no difference in the number of individuals who showed a higher than average plasma concentration for cotinine while smoking either of the two brands. These data suggest that smokers who obtain high cotinine plasma concentrations while smoking one brand also obtain high plasma cotinine concentrations while smoking the alternate brand. While smokers who obtain low plasma cotinine concentrations on one brand also have low plasma cotinine concentrations on the alternate brand. This suggestion could be tested by use of regression analysis.

Since these smokers had smoked an ultra low yield brand for at least three months and the average period of smoking an ultra low yield brand was six months', adaptation to the delivery of the brands should have been a minimal factor. This appears to be the case since there was no obvious difference in the number of cigarettes smoked per day resulting in a higher delivery for one of the two brands during the cross-over period.

Figure 2 is a regression analysis comparison of the plasma cotinine concentration obtained with Carlton brand smokers who were switched to the Barclay brand. The figure shows the slope of the regression line (R) and the standard error of R is given below the figure. In addition, the slope of the line which will provide a result that assures that 90% of the smokers studied were below this value is shown on the figure. These data indicate that 90% of the subjects studied had plasma cotinine concentrations less than or equal to 2.77 times their plasma cotinine concentration while smoking the Cambridge brand cigarettes. The data from the standard smoking machine tests, shown in Table 1., provides nicotine yield values for the Barclay brand cigarettes that is 1.6 times greater than the nicotine yield for the Cambridge cigarettes. Thus, the slope for the regression line which intercepts at the origin of 1.34 is less than the delivery difference one might expect for delivery in the individual smokers. The line with a slope of 2.77 is the line which provides for an uptake that is greater than that experienced by 90% of the smokers in the study. Therefore the maximum uptake for the Barclay brand is no greater than 2.77 times the plasma cotinine concentration while smoking the Cambridge brand. This increased nicotine uptake can be partially explained based upon the increased yield of the Barclay brand which is 1.6 times greater than the yield obtained by the Cambridge brand. These individuals normally smoked Carlton brand cigarettes. Certainly these data do not support the contention that smokers of Barclay brand cigarettes, which are equipped with the Actron filters, receive 4 to 8 times the nicotine and thus tar yield they experience with a cigarette equipped with a conventional ventilated filter, the Cambridge brand.

Similar data are presented in Figures 3, 4, and 5 where Barclay brand smokers and Carlton brand smokers were switched to the Cambridge brand. The analysis shown in Figures 3 and 4 support the conclusion that smokers obtain a similar amount of nicotine from the Carlton and Cambridge brands. The slope of the regression line was 0.85 and 0.93 for the two comparisons of these brands. The effects of brand change from Carlton to Barclay and from Barclay to Carlton are illustrated by Figures 2 and 3 (labeled as Barclay new brand or Carlton new brand). Thus the comparison is between the effects of a new experience with Carlton and Cambridge or Barclay and Cambridge.

The data illustrated in Figures 2 and 4 indicate that some smokers of Carlton brand cigarettes may have a higher plasma cotinine concentration than they obtain with Cambridge. When the Carlton smokers' cotinine concentrations were compared to their cotinine concentrations while smoking Cambridge brand cigarettes, the regression line slope, which passed through the origin, assured that 90% of the smokers would receive a yield no greater than the slope times the yield from the Cambridge brand. This regression slope is 2.00. However, when the Barclay brand smokers were switched to the Carlton brand this 90% regression line slope was 1.39 times the value for their experience with the Cambridge. Despite the fact that the Barclay brand yield by the standard smoking machine test is 1.8 times greater than the Carlton brand yield, 90% of the Barclay brand smokers, Figure 5, were below a regression line slope of 2.66 times the value obtained while smoking the Cambridge brand. When the Carlton brand smokers were switched to the Barclay brand, Figure 2, the 90% regression line slope was 2.77 times the value obtained from their Cambridge experience.

This difference could be related to differences in the easy-to-draw perception with the brands. Barclay brand is usually considered to be an easy-to-draw cigarette as compared to either the Carlton or Cambridge brands. Figures 2 and 4 contain the same individuals. Figure 4 represents the data from the baseline period when the Carlton smokers remained on their usual brand, while Figure 2 is derived from data obtained during the cross-over period where these Carlton smokers were switched to the Barclay brand. But, regardless of the cause, a few regular smokers of the Carlton brand obtained higher than expected nicotine uptake from their normal brand, Carlton, and also from the Barclay brand.

Additional analysis of the inter-individual variation is shown in Figure 6 and Figure 7. The data are plotted as an accumulative percent of the population sample that provide plasma cotinine at or below a given log of the plasma cotinine value. This plot provides two distinct curves for the smokers of the ultra low tar delivery brands tested. Smokers of the Carlton brand or the Cambridge brand which are equipped with conventional ventilated filters provide curves which overlap for either the 5 weeks or 4 weeks these brands were smoked. In the case of the Carlton smokers the comparisons between Carlton and Cambridge occurred over 4 weeks, two weeks smoking with each brand. In the case of the smokers who usually smoked the Barclay brand the comparisons between Carlton and Cambridge occurred over 5 weeks, three weeks on the Carlton brand and two weeks on the Cambridge brand. The subjects who usually smoked the Barclay brand are shown in Figure 6 while the subjects who usually smoked the Carlton brand are shown in Figure 7. Naturally, the curves providing the lowest log values were obtained with the Carlton and the Cambridge brands since these brands deliver 0.1 mg of nicotine or less. The curves which are shifted to the right, or to higher log values were obtained while the individuals were smoking the Barclay brand cigarettes. The Barclay brand cigarettes deliver 0.2 mg of nicotine.

In each case at population percentile levels one standard deviation above or below the mean value the smokers showed a higher plasma cotinine concentration while smoking the Barclay brand cigarette. This is to be expected since the Barclay brand potential delivery for nicotine is rated between 1.6 and 1.8 times greater by the standard smoking machine test (FTC method). It is interesting to note that over this range the two curves remain parallel. This observation supports the conclusion that the physiological processes by which the body produces and eliminates cotinine is not changed during the period of the study. If there was a change in the physiological processes one would expect the slope of these two curves to be different. This analysis is similar to that usually made of changes in the slope of the population percent response to the log dose plot for the dose response analysis done in pharmacological experiments.

During time periods when the subjects smoked either the Barclay brand or the Cambridge or Carlton brand there was a marked difference from the mean observed for one third of the smokers. This difference from the observed mean value is more than one standard deviation. The smokers with plasma cotinine concentrations more than one standard deviation below the mean plasma cotinine concentration value showed a smoking behavior that limited their intake of nicotine and thus tar. On the other hand the subjects with plasma cotinine concentrations which were more than one standard deviation above the average plasma

cotinine concentration show a smoking behavior that markedly increases their intake of both nicotine and tar. This sample of the population indicate that less than 20% of the population show this latter type of behavior and that the increased uptake of nicotine and thus tar provides overlapping data for all three brands tested.

Figure 8 and Figure 9 compares the shift along th plasma cotinine concentration axis which occurs with a change from either the Cambridge or Carlton brand to the Barclay brand. This change in plasma concentration is compared to the inter-individual difference in plasma concentration which occurs among smokers of any of the three brands. While the shift in the concentration curve occurs with the change to the higher potential nicotine delivery brand, the increase in plasma cotinine concentration among smokers of a particular brand is due to either an increase in nicotine and thus tar uptake related to more aggressive smoking behavior or due to an individual difference in metabolic handling of nicotine and cotinine. The inter-individual differences between the low intake and the high intake while smoking a particular brand was three times the change associated with the increase due to the increased potential nicotine delivery afforded by the Barclay brand.

DISCUSSION

The scattergram and the regression analysis support the conclusion that individual smokers obtain expected nicotine uptake from cigarettes based upon the relative standard smoking machine test yields. The regression analysis, when the slope is forced to pass through the origin, indicates that the individual smokers obtain 1.34 to 1.37 times more nicotine from Barclay brand than they did from the Cambridge brand. Forcing the slope through the origin is necessary since the zero point is the most valid point. Cotinine is only present as a result of nicotine metabolism. A review of Table 1. which provides the standard smoking machine test yields for the three brands indicates an increased nicotine delivery for the Barclay brand of 1.63 to 1.8 times larger than the other two brands. Ninety percent of the Barclay smokers had plasma cotinine concentrations less than 2.77 times their plasma cotinine concentrations while they were smoking Cambridge. Correction for the average number of cigarettes smoked per day did not affect the result because the average number of cigarettes smoked per day usually did not vary substantially with change from one brand to another. There was a significant variation in the average number of cigarettes smoked per day between individuals. However, on the average most individuals consumed 30 cigarettes per day.

Seventy-five per cent of the individuals maintained their relative percentile position regardless of the brand smoked. These individuals are found in either Quandrant II or IV of the scattergrams. The remaining 24% found in Quandrant I or III, are individuals who gave high plasma cotinine values while smoking one of the two brands. In no case was the brand specific high value found in more than 15% of the smokers tested. This value is found in Quandrant III and, since Barclay brand is known to deliver a higher quantity of nicotine, this result is not surprising. Several reasons may be valid to explain the difference seen in the smokers found in Quandrants II and IV. The smokers in Quandrant IV (47.5%) had lower than average plasma cotinine values regardless of the brand smoked while the smokers in Quandrant II (28.2%) had higher than average

concentrations for plasma cotinine with both brands smoked. An increase in the number of cigarettes smoked increases the plasma concentration of cotinine (See data in report of Gori and Lynch). Depth of inhalation and number of puffs are known factors that increase nicotine intake. Naturally, the suggestion of Benowitz, et al, 1982, that individual differences in rate of nicotine metabolism could be responsible for higher or lower than average plasma concentrations of cotinine, must be considered. Individuals who rapidly metabolize nicotine to cotinine, but more slowly metabolize cotinine might be expected to have higher cotinine plasma concentrations. This is especially true if the individual requires more nicotine because of the rapid metabolism. On the other hand, the individual who more slowly metabolizes nicotine to cotinine may be expected to have lower cotinine plasma concentrations. These metabolic differences made it mandatory that a self matching design be used in studies of nicotine and thus tar uptake by smokers.

Figures 2 and 4 show data obtained from smokers who are normally Carlton brand smokers, while Figures 3 and 5 show data obtained from smokers who are normally smokers of Barclay brand cigarettes. The obvious differences in the yields as indicated by the scatter in Figures 2 and 3 where the smokers experienced a new cigarette brand indicate the need for time to adapt to the new brand. The easy-to-draw effect appears to be causing less scatter in Figure 3, whereas, the scatter is quite marked when the Carlton brand smoker encounters the Barclay brand, shown in Figure 2. Nevertheless, when these ultra low yield smokers are compared against the Cambridge brand as a standard experience the individual differences in plasma cotinine concentration, as shown by the regression slope, is minimal.

It has been suggested that up to 40% of the smokers of ultra low tar cigarettes defeat the delivery system by abuse of the filter and air introduction system and thus receive more nicotine and tar than one would expect based upon standard smoking machine test yields of tar and nicotine. The individual with higher than average cotinine plasma concentration may achieve these values by defeating the delivery system. However a large percentage of the individuals studied achieve less than average nicotine intake from the delivery system based upon the plasma cotinine concentrations measured in this sample of ultra low tar cigarettes smokers.

The data presented supports the conclusion that brand differences as a factor which affects nicotine and tar uptake among ultra low tar cigarette smokers is a minimal factor. If some individuals defeat the filter mechanism which limits nicotine and tar delivery their actions are not brand specific and thus the problem is one that exists with the entire class of ventilated cigarettes. These data do not support the conclusion that 40% of the smokers defeat the filter system. The data supports a conclusion that almost fifty percent of the individuals who smoke the ultra low tar brands benefit from low nicotine and thus tar intake.

REFERENCES

BENOWITZ, Neal L.; Jacob, Peyton, III; Jones, Reese T.; and Rosenberg, J. Interindividual Variability in the Metabolism and Cardiovascular Effects of Nicotine in Man. J. Pharm. and Exper. Therap. 221:368-372, 1982.

WALD, Nicholas; Doll, Richard; and Copeland, Graham. Trends in tar, nicotine and carbon monoxide yields of UK cigarettes manufactured since 1934. Br. Med. J. (Clin. Res.), 1981. March 7; 282 (6266): 763-765.

(REFERENCES TO OTHER PERTINENT LITERATURE GIVEN IN PAPERS BY GORI AND LYNCH AND BY VAN ROSSUM AND DARBY)

FIGURE 1.

The points on the scattergram represent the plasma cotinine concentration obtained from the smoker during the period of smoking Barclay brand and Carlton brand cigarettes. Numbers larger than one indicate the number of smokers who gave the same plasma cotinine concentration. The scattergram is divided into four quadrants by drawing a line at the average plasma cotinine concentration obtained from the smokers while they were smoking either Barclay or Carlton brand cigarettes. Thus quadrant I contains those smokers who demonstrated higher than average values while smoking Carlton brand cigarettes and lower than average values while smoking Barclay brand cigarettes. Those smokers who demonstrated higher than average values while smoking either Barclay brand or Carlton brand cigarettes are located in quadrant II. Quadrant III contains those smokers who demonstrated higher than average values while smoking Barclay brand cigarettes while demonstrating lower than average values while smoking the Carlton brand cigarettes. The smokers in quadrant IV demonstrated lower than average plasma concentrations of cotinine while smoking either Barclay or Carlton brand cigarettes. The percent of the individuals contained in a particular quadrant is listed in Table 2.

FIGURE 1

CARLTON AND BARCLAY SMOKERS

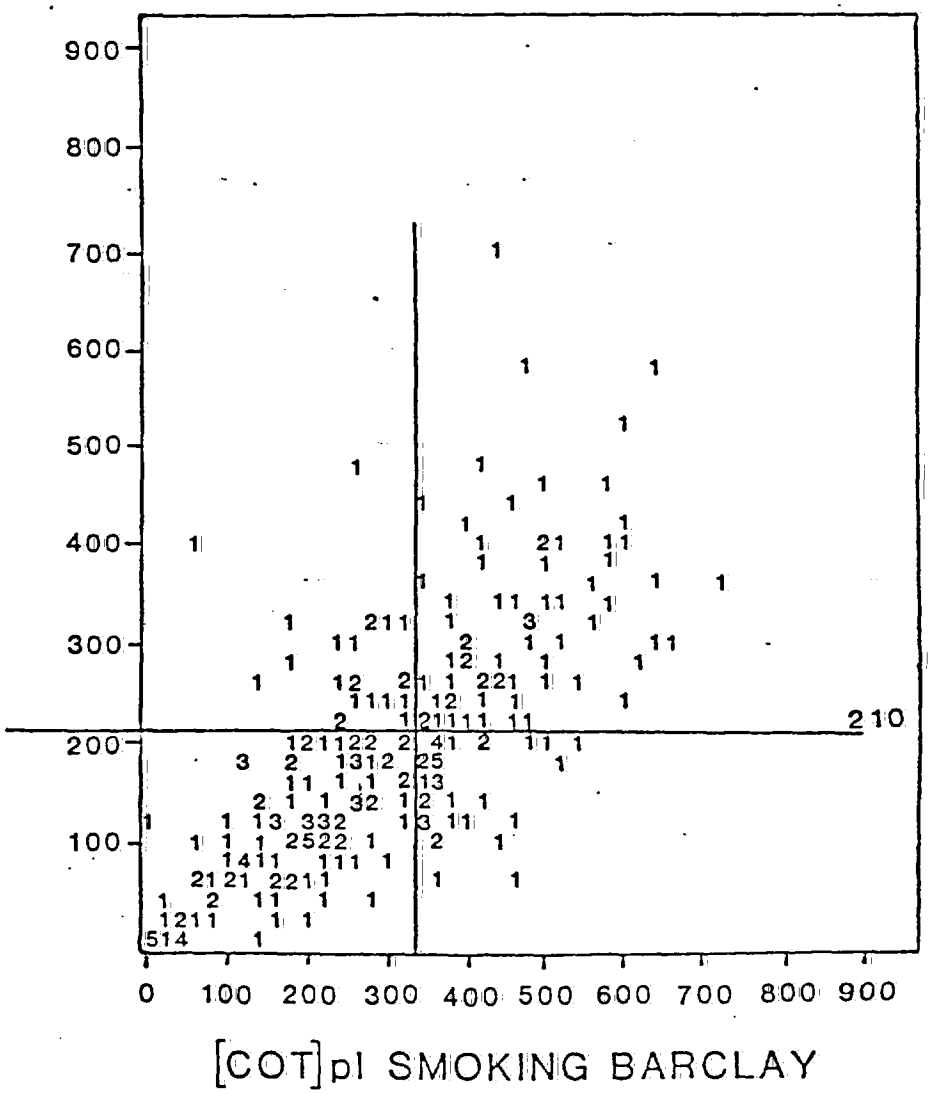
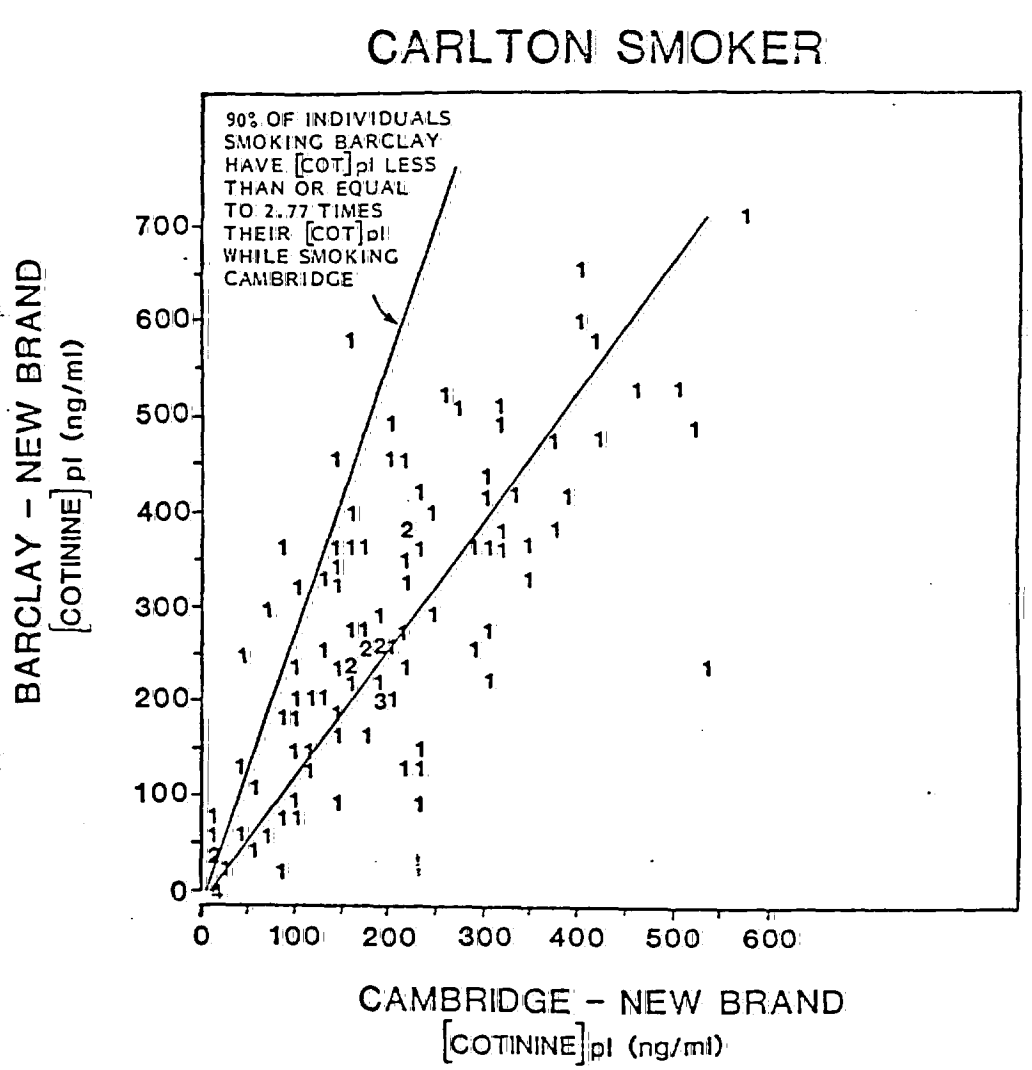


FIGURE 2.

Figure 2 provides a regression analysis comparison of the plasma cotinine concentration obtained while the smokers were smoking Barclay brand cigarettes as compared to their plasma cotinine concentration while they were smoking the Cambridge brand cigarettes. The slope of the line illustrates the difference in the relative uptake of nicotine and thus tar between the brands compared. A slope is also provided which assures that 90% of the individuals studied would have a value less than 2.77 times the plasma concentration obtained while smoking the Cambridge brand. Other pertinent data are given in the legend on the figure.

FIGURE 2



CORRELATION COEFFICIENT (R)	= .74
NO. OF OBSERVATIONS	= 106
STANDARD ERROR OF R	= .06

LINEAR REGRESSION

SLOPE	= .98
Y-AXIS INTERCEPT	= 98

REGRESSION THROUGH ORIGIN

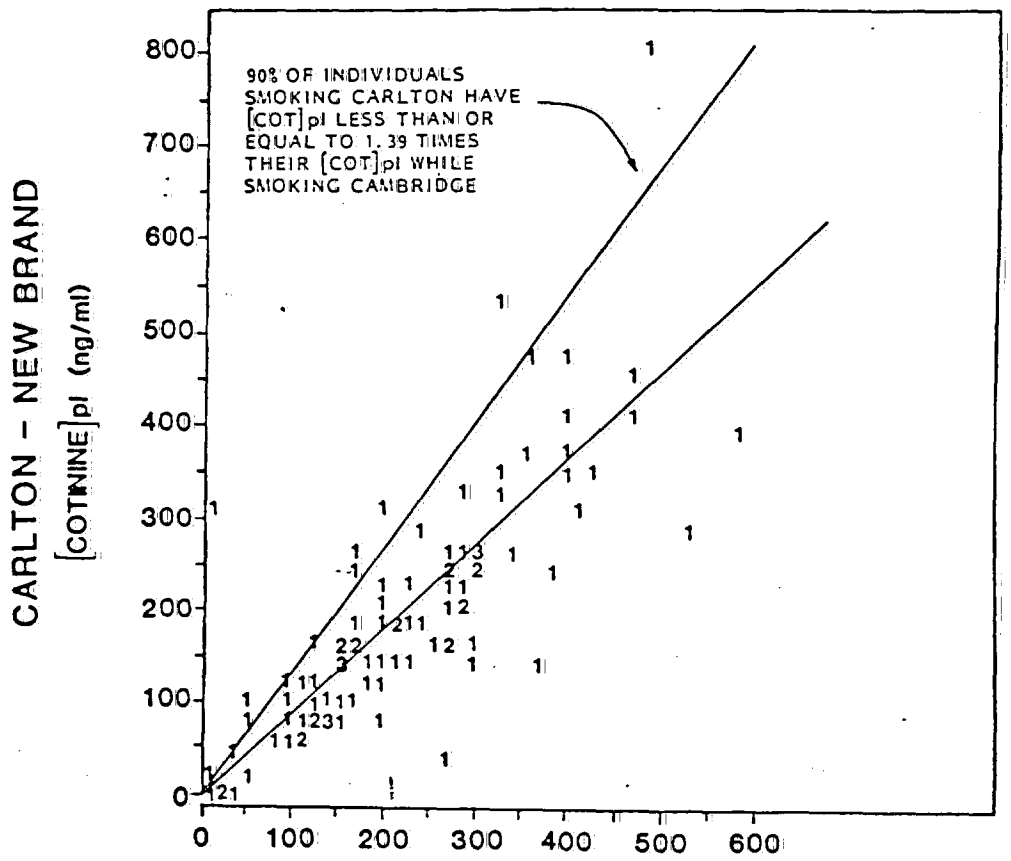
SLOPE (0 INTERCEPT ASSUMED)	= 1.34

FIGURE 3.

See text and the legend for figure 2 for pertinent information.

FIGURE 3

BARCLAY SMOKER



CARLTON - NEW BRAND
[COTININE]pl (ng/ml)

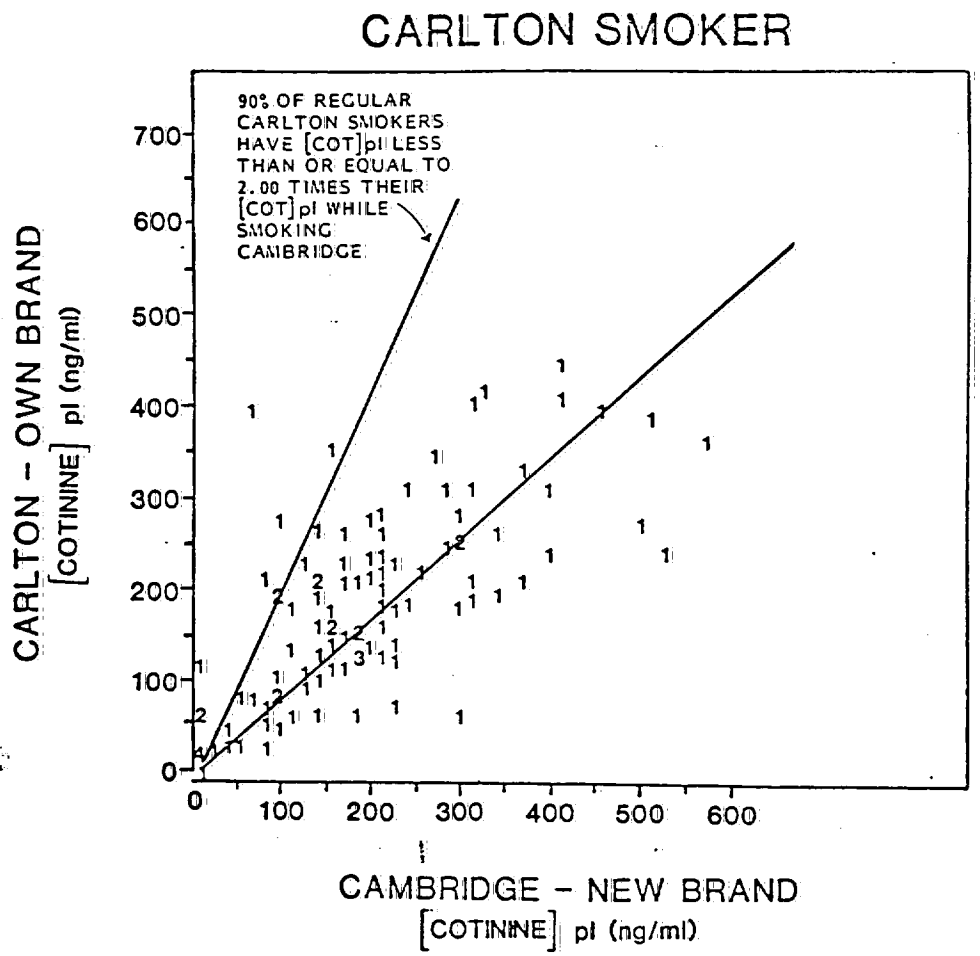
CAMBRIDGE - NEW BRAND
[COTININE]pl (ng/ml)

CORRELATION COEFFICIENT (R)	= 0.79	LINEAR REGRESSION SLOPE	= 0.85
NO. OF OBSERVATIONS	= 98	Y - AXIS INTERCEPT	= 24
STANDARD ERROR OF R	= 0.06	SLOPE 0 INTERCEPT ASSUMED (REGRESSION THROUGH ORIGIN)	= 0.93

Figure 4.

See text and the legend for figure 2 for pertinent information.

FIGURE 4



CORRELATION COEFFICIENT (R)	= 0.70	LINEAR REGRESSION SLOPE	= 0.60
NO. OF OBSERVATIONS	= 106	Y - AXIS INTERCEPT	= 69
STANDARD ERROR OF R	= 0.07	SLOPE 0 INTERCEPT ASSUMED (REGRESSION THROUGH ORIGIN)	= .85

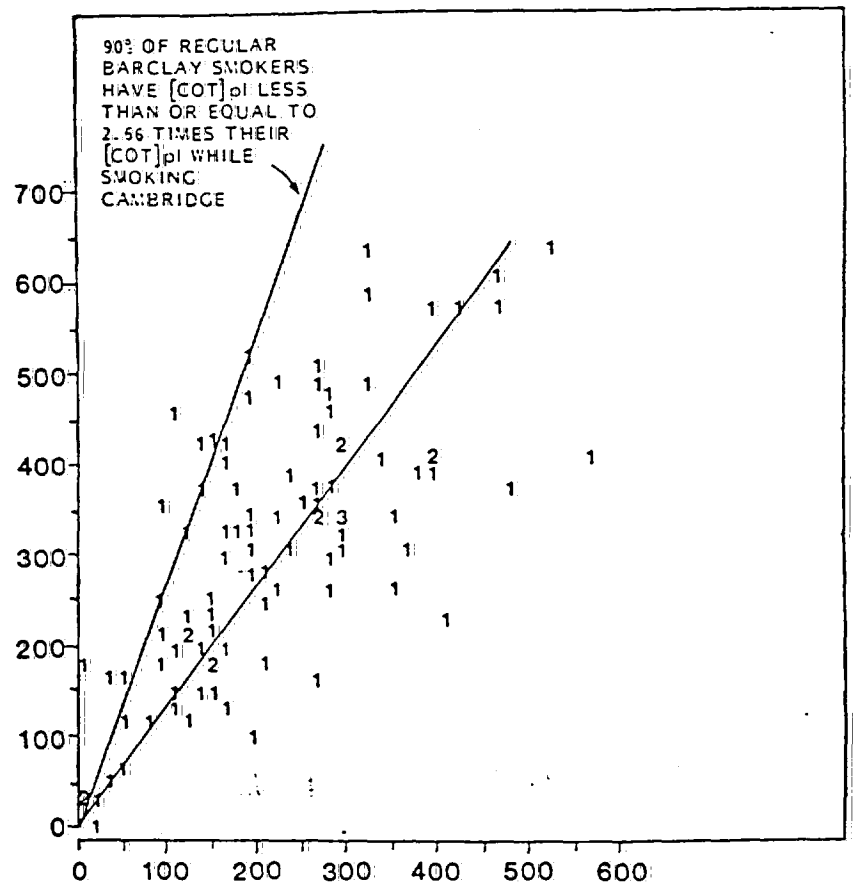
10050630 39

Figure 5.

See text and the legend for figure 2 for pertinent information.

FIGURE 5

BARCLAY SMOKER



CORRELATION COEFFICIENT (R)	= .69
NO. OF OBSERVATIONS	= 98
STANDARD ERROR OF R	= .07

LINEAR REGRESSION

SLOPE	= .84
Y AXIS INTERCEPT	= 137

REGRESSION THROUGH ORIGIN

SLOPE (0 INTERCEPT ASSUMED) = 1.33

Figure 6.

This figure presents a plot of the cumulative percentile of the population vs. the log of the plasma cotinine concentration. These data illustrate the large inter-individual differences seen in uptake of nicotine and thus tar as measured by analysis of plasma for cotinine concentration. While it is reasonable to assume that the increased uptakes are due to smoking behavior differences, it is not unreasonable to assume that individual differences in rate of metabolism of nicotine to cotinine could account for some to the increased cotinine concentration. However, since the curves obtained with Carlton and Cambridge on the one hand and with Barclay on the other are parallel, there are no individual differences in the matabolic handling of nicotine occurring during the study period. These data support the conclusion that the Actron Filter cigarettes, Barclay, are similar in their delivery of nicotine and thus tar to other conventional air dilution filter cigarette deliveries, i.e., the delivery of Carlton and Cambridge.

FIGURE 6

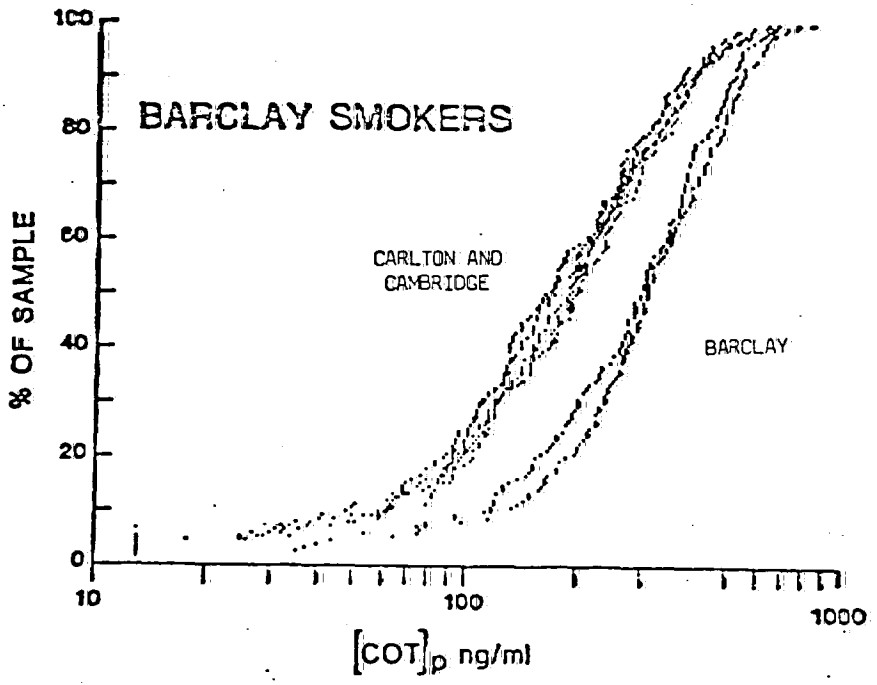


Figure 7.

This figure presents data similar to that provided in Figure 6. however, in this case the smokers represent the individuals who normally smoked the Carlton brand cigarettes. The curves obtained with the Carlton brand smokers are not different from the curves shown for Barclay brand smokers in Figure 6.

FIGURE 7

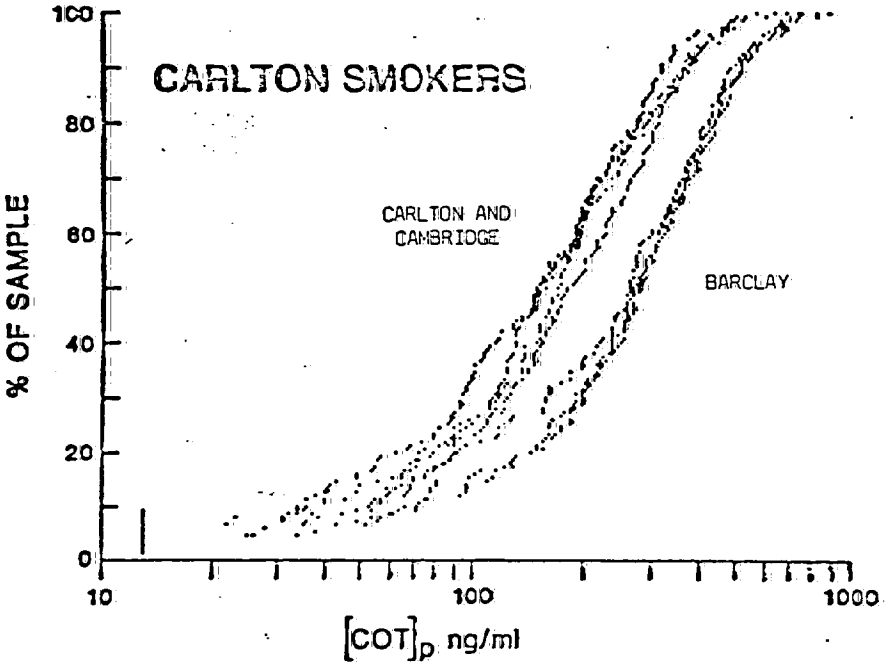


Figure 8.

This figure presents the percentile data plotted vs. the plasma cotinine values. The shift to the right is caused by the higher potential nicotine delivery of Barclay. This shift is only one-third the increase caused by smoking behavior differences. The increase in plasma cotinine concentration based upon inter-individual differences is 320 ng/ml over a two standard deviation range. A switch from Barclay provided an intra-individual difference of 110 ng/ml over this two standard deviation range.

FIGURE 8

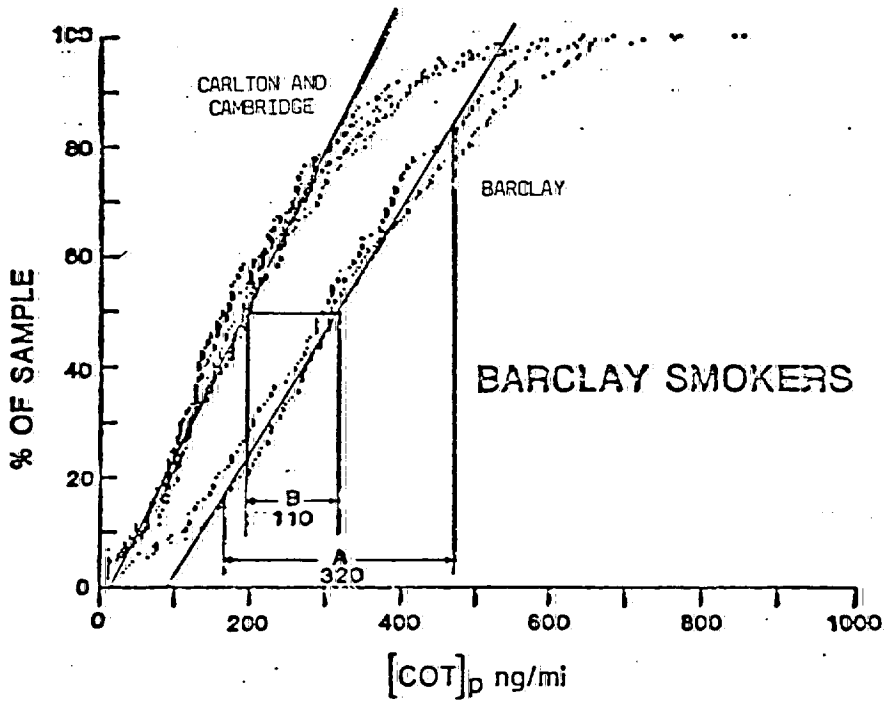


Figure 9

This figure presents data similar to that shown in Figure 8 however in this case the Carlton smokers are shown. Notice the similar smoking behavioral effects and the similar shift due to the increased potential nicotine delivery seen with the Barclay brand cigarette. There is no difference in delivery seen with the population sample of Carlton smokers and the population sample of Barclay smokers.

FIGURE 9

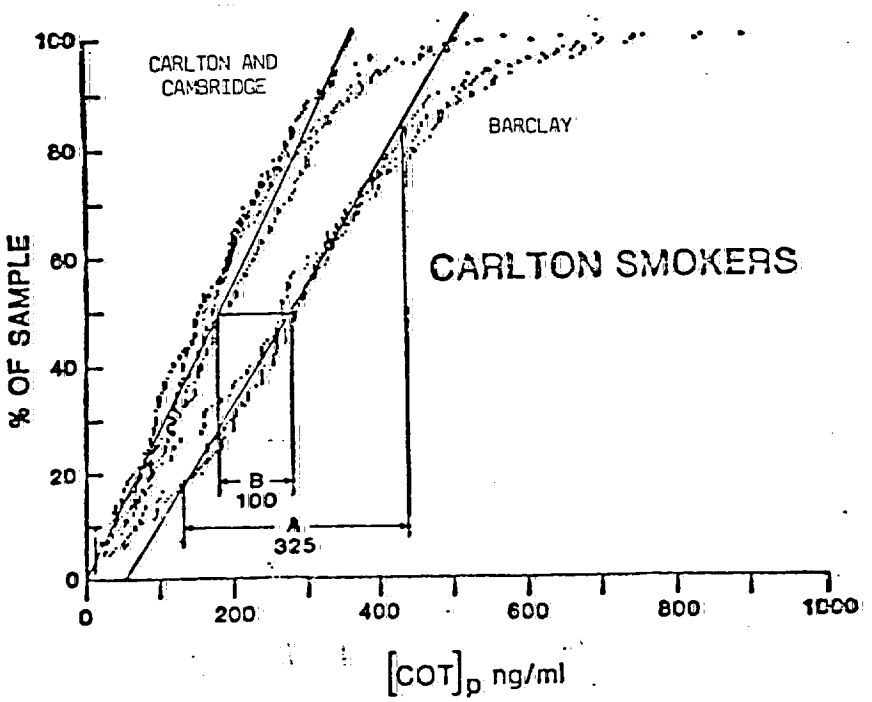


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TABLE 1.

NICOTINE AND TAR YIELD DERIVED BY STANDARD FTC TEST METHOD.

BRAND TESTED	BATCH	MILLIGRAMS/CIGARETTE TAR	NICOTINE
BARCLAY	IXL	0.9	0.18
CARLTON	00025	0.5	0.10
CAMBRIDGE	EB	0.6	0.11

In each case the stardard deviation of the measurement was 0.02

Table 1 provides the analytical data for the batch code of the brand listed. Only cigarettes from one batch of each brand were used in the study. The batch represented 85 mm length, filter, soft pack cigarettes. With the air introduction and the filtration provided, the tar measurements are difficult. However, each of the brands tested provided less than 1 mg. tar.

TABLE 2.

	Number of Individuals	Percent of the Total Number
QUADRANT I	23	9.3
QUADRANT II	70	28.2
QUADRANT III	37	15.0
QUADRANT IV	117	47.5

Table 2. provides the number and the percentage of the total number of individuals studied found in each of the four quadrants delineated in Figure 1. The average plasma cotinine concentration for smokers of Carlton brand cigarettes was 210 ng/ml. The average plasma cotinine concentration for smokers of Barclay brand cigarettes was 340 ng/ml.

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